

In re Application of: Brackett N. L., et al.
Confirmation No: 6890
Application No.: 10/748,637
Examiner: SCHUBERG, L. J.
Response to June 13, 2006 Office Action
Page- 5 -

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REMARKS

Claims 1-19 are pending in the application. Claim 4 has been amended to include the full name of the abbreviation "SCI." No new matter has been added by virtue of this amendment and its entry is respectfully requested.

Attached hereto, are the 37 C.F.R. § 1.1.32 Declarations (as "Exhibit A") of the inventors which further explain the differences between the instant invention and the cited references. Consideration and entry is respectfully requested.

Claim Objections

Claim 4 is objected to for recitation of SCI. In response Applicants have amended claim 4 to recite the full terminology, i.e. "spinal cord injury." No new matter has been added by virtue of this amendment and its entry is respectfully requested.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant objection.

Claim Rejections Under 35 U.S.C. § 102

Claims 1, 2, 5, 6, 8-19 are rejected under 35 U.S.C. § 102(b) as being anticipated by Alexander et al (US 6,180,355 B1).

Applicants respectfully traverse.

Applicants invention is directed, in part, to method of increasing motility of sperm, by providing from a subject a biological sample comprising sperm and at least one cytokine; and contacting the biological sample with an agent that inactivates or reduces the biological activity of the at least one cytokine selected from the group consisting of TNF α , IL1 β , and IL6.

{WP333289,1}

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Alexander et al., neither teaches nor discloses methods of increasing sperm motility. Alexander et al., discusses diagnosing of CPPS. There is no discussion or teaching that administration of anti-cytokine antibodies or agents increase sperm motility. Furthermore, treatment of sexual dysfunction by administering anti-TNF α antibodies with a patient suffering from CPPS has no bearing on treating fertility, i.e. sexual function vs. fertility. Alexander et al., neither teaches nor discloses treatment of actual semen samples with any anti-cytokine agents. In contrast, Alexander et al., discusses systemic administration of an anti-TNF- α antibody.

Applicants further discuss in detail in the 37 C.F.R. Rule 1.132 Declarations (Exhibit "A") filed herewith, that Alexander et al. neither teaches nor discloses the instant invention.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claim Rejections Under 35 U.S.C. § 103

Claims 1-6 and 8-19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Alexander et al. (US 6,180,355 B1) in view of Basu et al (Journal of Andrology, 2002).

Applicants respectfully traverse.

Alexander has been discussed above. Alexander et al does not teach or disclose the instant invention. Furthermore Alexander discusses sexual dysfunction which is completely different to infertility and sperm mobility. There is no motivation to combine Alexander et al., with Basu et al., as each discuss different conditions and diagnosis of CPPS as discussed by Alexander would not result in a method of treatment infertility as taught by the instant invention. Further, as stated by the inventors in the 37 C.F.R. Rule 1.132 Declaration, Basu is a co-inventor and the conception of the instant application preceded the Basu publication. As such, Basu et al is not a proper reference.

{WP333289.1}

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In view of the foregoing and Applicants Declaration, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claims 1, 2, 5-19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Alexander et al. (US 6,180,355 B1) in view of Faber et al. (Obstetrics and Gynecology 2001) and Slesarev (US 5,834,435).

Applicants respectfully traverse.

Applicants have discussed Alexander et al. Faber does not teach or disclose a method of treating sperm mobility using anti-cytokine agents. Faber discusses endometriosis-associated infertility in females. There is no teaching or disclosure in Faber that would motivate one of ordinary skill in the art to treat male infertility nor combine the teachings of Alexander with Faber. Faber does not make up for the deficiencies of Alexander et al. Neither treats male infertility. Slesarev et al., also fails to make up for the deficiencies of Alexander and Faber. Slesarev does not teach or disclose treatment of male infertility. Vaginal application of a compound that inhibits TNF α is irrelevant to treating male infertility.

The Examiner, on page 6, sets out the reasoning for the rejection based on cited references "to treat endometriosis in women...." Applicants submit that treating male infertility as taught by Applicants is not obvious in view of the cited references standing alone or taken together. Further discussion is provided by the declarations of the inventors, filed herewith.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

{WP333289;1}

In re Application of: Brackett N. L., et al.
Confirmation No: 6890
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CONCLUSION

Applicants respectfully request entry of the foregoing remarks and reconsideration and withdrawal of all rejections. It is respectfully submitted that this application with claims 1-19 define patentable subject matter and is in condition for allowance. Accordingly, Applicant respectfully requests allowance of these claims.

This response is being timely filed within the shortened statutory period and, as such, Applicants believe that no fees are due. Although, Applicants believe that no extensions of time are required with submission of this paper, Applicants request that this submission also be considered as a petition for any further extensions of time if necessary. The Commissioner for Patents and Trademarks is hereby authorized to charge the amount due for any retroactive extensions of time and any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing or during prosecution of this application to Deposit Account No. 50-0951.

Respectfully submitted,
AKERMAN SENTERFITT

Date: September 13, 2006


Nicholas A. Zachariades, Ph.D.
Reg. No. 56,712
AKERMAN SENTERFITT
P.O. Box 3188
West Palm Beach, FL 33402-3188
Tel: 561-653-5000

Docket No. 7230-9

{WP333289;1}

SEP 13 2006

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EXHIBIT "A"

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Bruckart N. L. et al.
 Application No.: 10748,637
 Date Filed: December 10, 2003
 Pat: INCREASING SPERM MOTILITY

Confirmation No: 6890

Examiner: SCHUBERT, L. J.

Group: 1631

Communication Under 37 CFR 1.8(d)
 I hereby certify that the correspondence is being
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 Sept 13, 2006

 Nancy L. Bruckart
 Inventor & Zealot

INCHER L. 112 DECLARATION

Via Facsimile No. 571-271-8109

Mail Stop Amendment
 Commissioner for Patents
 P.O. Box 1400
 Alexandria, VA 22313-1400

I, Nancy L. Bruckart, declare as follows:

- I am one of the named inventors and am familiar with patent application No. 10748,637 entitled "INCREASING SPERM MOTILITY" (hereinafter the '637 application) and the subject matter described therein.
- I hold a Ph.D. in Behavioral Neuroscience and an HCLD in Audiology. I am presently employed as a Research Associate Professor of Neurological Surgery and Urology, University of Miami Miller School of Medicine. I have worked in the field of reproductive

Nancy L. Bruckart

Sep. 12, 2006 12:35PM

No. 0420 P. 2

T-425 P.10/40 F-719

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RULE 132 DECLARATION
In re Application of: Brackefit N. L., et al.
Confirmation No.: 6890
Application No.: 10748,617
Page 2 -

biology for 20 years. My expertise is in Andrology and male infertility, specifically infertility of men with spinal cord injury.

3. I have authored or coauthored more than 50 scientific papers.
4. I have reviewed this Office Action dated June 17, 2006 and references cited therein. I have been asked by patent counsel Zuckerman to provide an explanation based on the claimed invention showing that the subject matter of the claims differs from the cited art. Independent claim 1 is copied below.

Claim 1. A method of increasing motility of sperm, the method comprising the steps of:
a) providing, from a subject a biological sample comprising sperm and at least one cytoskeleton and

b) contacting the biological sample with an agent that inactivates or reduces the biological activity of the at least one cytoskeleton selected from the group consisting of TNF α , IL-1 β , and IL-6.

5. The Examiner has rejected claims 1, 2, 3, & 8-19 as rejected under 35 U.S.C. §102(b) as being anticipated by Alexander et al. (US 6,180,215 B1). The Examiner has also rejected claims 1-6 and 8-17 under 35 U.S.C. §103(a) as being unpatentable over Alexander et al. (US 6,180,215 B1) in view of Blaauw et al. (Journal of Andrology 2002). Claims 1, 2, and 5-

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19 were rejected under 35 U.S.C. §101(a) as being unpatentable over Alexander et al. (US 6,180,755 B1) in view of Fisher et al. (Obstetrics and Gynecology 2001) and Shearer (US 5,814,735).

6. First, I will discuss the Alexander et al. (US 6,180,755 B1) reference and why this patent does not teach or disclose the instant invention.

The Alexander patent discusses the use of cytokines as indicators to help diagnose chronic pelvic pain syndrome (CPPS). Simply put, Alexander discusses that cytokines in the seminal plasma can be used as "indicators or confirmatory indicators" of CPPS or an associated disorder. Alexander defines CPPS as the presence of leukocytes in the expressed prostatic secretions or by sediment found in a urine sample collected following a prostate massage. Alexander interchanges the terms "CPPS" and "extrauterine prostatitis" in the text of their patent. Alexander discusses the condition(s) with respect to sexual function.

Alexander discusses a "method of treating a condition associated with elevated levels of a cytokine, such as TNF-alpha, in seminal plasma, comprising administering a therapeutically effective amount of an anti-cytokine...". Further, all treatments taught in the Alexander patent are by systemic administration of oral or parenteral agents.

The instant invention is not taught or disclosed by Alexander et al.

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RUFB 112 DECLARATION
In re Application of: Bracken N. L. et al.
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Application No.: 107448,617
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The Examiner wrongly interprets Alexander's teaching, i.e., the Examiner assumes that:
any falls or examples in the Alexander patient, nor in this assumption correct in the medical field.
Our patient addresses low sperm motility, not a condition of sexual dysfunction.

As described, Alexander uses cytokines as "indicators or confirmatory indicators" of
CPPS. In contrast to the Alexander patient, our patient does not use cytokines to *diagnose* a
disease. Instead, our patient states that cytokines are *agents* in the semen which act immediately
on sperm cells to reduce their motility in the capsules. Prior to contact with the semen cytokines,
sperm motility is normal or near normal.

Alexander discusses a "method of treating a condition associated with elevated levels of a
cytokine, such as TNF-alpha, in seminal plasma, comprising administering a therapeutically
effective amount of an anti-cytokine...". The "method" clearly referred to in the Alexander
patent is CPPS or a similar condition, not the presence of the cytokines themselves, as is the case
in our patient. Our target group is not men with CPPS, but men with spinal cord injury. Our
patient does not claim that CPPS causes decreased sperm motility.

All treatments taught in the Alexander patent are by systemic administration of oral or
parenteral agents. In the Alexander patient, there is no provision for treating the semen. In the

parasexual

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In re Application of: Drackett N. L. et al.
Continuation No. 6890
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in medical field, there is no basis for asserting that treating the seminal will improve CPPS. Our patent provides for treating the seminal to improve the condition of low sperm motility in men with spinal cord injury.

7. Second, I will discuss the basis of art, reference and why this reference does not teach or disclose the instant invention.

Some of the Examiner's objections are based on publications by Basu. The Examiner believes that these Basu publications preceded the present application. Basu is one of our co-inventors. It is my understanding that the invention disclosure date is the key date. The invention disclosure was submitted to the University of Miami on July 11, 2002. The date of conception is listed on the Invention Disclosure form was Jan. 12, 2001. The examiner asserts that "use of ordinary skill in the art would have been required to use the method of Alexander because Alexander discloses that the method can be used to treat conditions associated with elevated levels of a cytokine."

Once again, we assert that the method referred to treats conditions such as CPPS by administration of anti cytokine agents orally or parenterally. Our method treats an unrelated condition, low sperm motility, by the addition anti cytokine agents to the seminal plasma *in vitro* (see above).

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RULE 111 DECLARATION
In re Application of: Brackell N. L., et al.
Confirmation No.: 6890
Application No.: 107748, 637
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Fees: 6-

8. Third, I will discuss the Fisher et al. reference and why this reference gives no teach or disclose the test and invention. The reference discusses the occurrence of certain cytokines in the peritoneal fluid of women with endometriosis and their effect on the binding of cytokines in the same cell culture. It discusses infertility in women caused or reduced by endometriosis

The impact of biodiversity is not taught or disclosed by Huber et al.

Father does not measure or evaluate sperm motility. It measures the interaction of sperm with a certain portion of the uterus and notes that women with endometriosis may have elevated levels of crystalline in their peritoneal fluid and fallopian tubes that may interfere with sperm - zona binding. There is no suggestion on their part or reasonable medical conclusion that can be reached that reaches that treating sperm in the ejaculate will or may remedy this affliction of the female reproductive tract.

The examinee states that peritoneal fluid is produced from the reproductive tract. This is factually incorrect.

9. Fourth, I will discuss the *Stargazer* reference and why this reference does not teach or dissects the instant invention. The reference discusses the systemic effects of TNF-alpha, in a variety of cells and often heat conditions as well as pit term labor and the role of a certain neumaryl dipeptide (QRD/P) in modulating these effects, specifically the synthesis of

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RULE 112 DECLARATION
In re Application of: Blenckert N. L. et al.
Confirmation No: 6890
Application No.: 10748637
Page - 7 -

prostaglandin E2. This probable matamyl peptide is a component of the bacterial cell wall of normal vaginal flora and may also be found in human and toxic fluid.

The instant invention is not taught or disclosed by Steaure et al:

Neither male infertility nor low sperm motility or any other sperm abnormality is mentioned or suggested in the discussion of the effects of TNF-alpha or the modulation of its effects. Steaure proposed the vaginal application of GMFD as a treatment of pre-term labor and of "pregnancy toxicity". In another instance, the vaginal application seems to be factuated with all other methods of administration, (oral, topical, rectal, and as a food supplement) to achieve systemic absorption. In this setting, we do not agree, that "one of ordinary skill in the art would have had a reasonable expectation of success [in creating low sperm motility by our method] because Steaure had previously administered vaginally a compound that inhibits TNF-alpha". Again, we propose treating a local condition, low sperm motility, rather than a systemic condition.

10. I further state that all statements made herein are of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with my knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United

STATEMENT

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RULE 132 DECLARATION
In re Application of: Bruckel, N. L., et al.
Confirmation No. 6830
Application No.: 10748,637
Page : 8 -

States Costs, and that such willful false statements may jeopardize the validity of the application
or any patent issued thereon.

Nancy L. Bruckel Sept 12, 2006
Dr. Nancy L. Bruckel, Ph.D. HCQD

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SEP. 12, 2006 12:36PM
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EXHIBIT "A"

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Brackett N. L., et al. Confirmation No: 6890

Application No.: 10/748,637 Examiner: SCHUBERG, L. J.

Date Filed: December 30, 2003 Group: 1651

For: INCREASING SPERM MOTILITY

CERTIFICATE UNDER 37 CFR 1.8(a)
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Sept 13, 2006Nic
Nicholas A. Zachanades

Reg. No. 56,712

37 C.F.R. 1.132 DECLARATIONVia Facsimile No. 571-273-8300

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Sarmistha Basu, declare as follows:

1. I am one of the named inventors and am familiar with patent application No. 10/748,637 entitled "INCREASING SPERM MOTILITY" (hereafter the '637 application) and the subject matter described therein.

2. I hold a Ph.D. in Science (Biochemistry). I am presently employed as Program Manager at Dow Pharmaceutical Sciences, Inc., Petaluma, California for last 5 years. I have worked in the field of Biochemistry for 7 years.

3. I have authored or coauthored more than 6 scientific papers.

(WP333261;1)

RULE 132 DECLARATION

In re Application of: Brackett N. L., et al.
Confirmation No: 6890
Application No.: 10/748,637
Page - 2 -

4. I have reviewed the Office Action dated June 13, 2006 and references cited therein. I have been asked by patent counsel Zachariades to provide an explanation based on the claimed invention showing that the subject matter of the claims differs from the cited art. Independent claim 1 is copied below.

Claim 1. A method of increasing motility of sperm, the method comprising the steps of:

- a) providing from a subject a biological sample comprising sperm and at least one cytokine; and
- b) contacting the biological sample with an agent that inactivates or reduces the biological activity of the at least one cytokine selected from the group consisting of TNF α , IL1 β , and IL6.

5. The Examiner has rejected claims 1, 2, 5, 6, 8-19 are rejected under 35 U.S.C. §102(b) as being anticipated by Alexander *et al.* (US 6,180,355 B1). The Examiner has also rejected claims 1-6 and 8-19 under 35 U.S.C. §103(a) as being unpatentable over Alexander *et al.* (US 6,180,355 B1) in view of Basu *et al.* (*Journal of Andrology* 2002). Claims 1, 2, and 5-19 were rejected under 35 U.S.C. §103(a) as being unpatentable over Alexander *et al.* (US 6,180,355 B1) in view of Faber *et al.* (*Obstetrics and Gynecology* 2001) and Slesarev (US 5,834,435).

{WF333251:1}

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In re Application of: Brackett N. L., et al.
Confirmation No: 6890
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6. First, I will discuss the Alexander *et al* (US 6,180,355 B1) reference and why this patent does not teach or disclose the instant invention.

The Alexander patent discusses the use of cytokines as indicators to help diagnose chronic pelvic pain syndrome (CPPS). Simply put, Alexander discusses that cytokines in the seminal plasma can be used as "indicators or confirmatory indicators" of CPPS or an associated disorder. Alexander defines CPPS as the presence of leukocytosis in the expressed prostatic secretions or by sediment found in a urine sample excreted following a prostate massage. Alexander interchanges the terms "CPPS" and "chronic prostatitis" in the text of their patent. Alexander discusses the condition(s) with respect to sexual function.

Alexander discusses a "method of treating a condition associated with elevated levels of a cytokine, such as TNF-alpha, in seminal plasma, comprising administering a therapeutically effective amount of an anti-cytokine..." Further, all treatments taught in the Alexander patent are by systemic administration of oral or parenteral agents.

The instant invention is not taught or disclosed by Alexander et al.

The Examiner wrongly interprets Alexander's teaching, i.e., the Examiner assumes that effects on sexual function also occur to fertility. The Examiner's assumption is not supported by any facts or examples in the Alexander patent, nor is this assumption correct in the medical field. Our patent addresses low sperm motility, not a condition of sexual dysfunction.

{WP333251:1}

RULE 132 DECLARATION

In re Application of: Bracken N. L., et al.

Confirmation No: 6890

Application No.: 10/748,637

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As described, Alexander uses cytokines as "indicators or confirmatory indicators" of CPPS. In contrast to the Alexander patent, our patent does not use cytokines to *diagnose* a disease. Instead, our patent states that cytokines are agents in the semen which act immediately on sperm cells to reduce their motility in the ejaculate. Prior to contact with the semen cytokines, sperm motility is normal or near normal.

Alexander discusses a "method of treating a condition associated with elevated levels of a cytokine, such as TNF-alpha, in seminal plasma, comprising administering a therapeutically effective amount of an anti-cytokine..." The "condition" clearly referred to in the Alexander patent is CPPS or a similar condition, not the presence of the cytokines themselves, as is the case in our patent. Our target group is not men with CPPS, but men with spinal cord injury. Our patent does not claim that CPPS causes decreased sperm motility.

All treatments taught in the Alexander patent are by *systemic administration* of oral or parenteral agents. In the Alexander patent, there is no provision for treating the semen. In the medical field, there is no basis for assuming that treating the semen will improve CPPS. Our patent provides for treating the semen to improve the condition of low sperm motility in men with spinal cord injury.

{WP333251:1}

RULE 132 DECLARATION

In re Application of: Brackett N. L., et al.
Confirmation No: 6890
Application No.: 10/748,637
Page - 5 -

7. Second, I will discuss the Basu *et al.* reference and why this reference does not teach or disclose the instant invention.

Some of the Examiner's objections are based on publications by Basu. The Examiner believes that these Basu publications preceded the patent application. Basu is one of our co-inventors. It is my understanding that the invention disclosure date is the key date. The invention disclosure was submitted to the University of Miami on July 31, 2002. The date of conception as listed on the Invention Disclosure form was Jan. 12, 2001. The examiner asserts that "one of ordinary skill in the art would have been motivated to use the method of Alexander because Alexander discusses that the method can be used to treat conditions associated with elevated levels of a cytokine....."

Once again, we assert that the method referred to treats conditions such as CPPS by administration of anti cytokine agents orally or parenterally. Our method treats an unrelated condition, low sperm motility, by the addition anti cytokine agents to the seminal plasma in vitro (see above).

8. Third, I will discuss the Faber *et al.* reference and why this reference does not teach or disclose the instant invention. The reference discusses the occurrence of certain cytokines in the peritoneal fluid of women with endometriosis and their effect on the binding of sperm to the zona pellucida. It discusses infertility in women caused or related to endometriosis.

The instant invention is not taught or disclosed by Faber *et al.*

Faber does not measure or evaluate sperm motility. It measures the interaction of sperm with a certain portion of the ovum and notes that women with endometriosis may have elevated

{WP333251:1}

RULE 132 DECLARATION

In re Application of: Brackett N. L., et al.
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Application No.: 10/748,637
Page - 6 -

levels of cytokines in their peritoneal fluid and fallopian tubes that may interfere with sperm - zona binding. There is no suggestion on their part or reasonable medical conclusion that can be reached that teaches that treating sperm in the ejaculate will or may remedy this affliction of the *female reproductive tract*.

The examiner states that peritoneal fluid is produced from the reproductive tract. This is factually incorrect.

9. Fourth, I will discuss the Slesarev reference and why this reference does not teach or disclose the instant invention. The reference discusses the systemic effects of TNF-alpha in a variety of toxic and often fatal conditions as well as pre term labor and the role of a certain muramyl dipeptide (GMDP) in modulating these effects, specifically the synthesis of prostaglandin E2. This probiotic muramyl peptide is a component of the bacterial cell wall of normal vaginal flora and may also be found in human amniotic fluid.

The instant invention is not taught or disclosed by Slesarev *et al*:

Neither male infertility nor low sperm motility or any other sperm abnormality is mentioned or suggested in the discussion of the effects of TNF-alpha or the modulation of its effects. Slesarev proposed the vaginal application of GMPD as a treatment of pre term labor and of "pregnancy toxicity". In another instance, the vaginal application seems to be included with all other methods of administration, (oral, topical, rectal, and as a food supplement) to achieve systemic absorption. In this setting, we do not agree that "one of ordinary skill in the art would have had a reasonable expectation of success [in treating low sperm motility by our method] because Slesarev had previously administered vaginally a compound that inhibits TNF-

(WP333261;1)

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RULE 132 DECLARATION

In re Application of: Brackett N. L., et al.

Confirmation No: 6890

Application No.: 10/748,637

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SEP 13 2006

alpha". Again, we propose treating a local condition, low sperm motility, rather than a systemic condition.

10. I further state that all statements made herein are of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with my knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Sarmistha Basu

Dr. Sarmistha Basu

09/13/06

Date

(WP333261.1)

EXHIBIT "A"

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Brinkhoff, N. L., et. al.
Application No.: 10748,637
Date Filed: December 10, 2001
For: INCRASING SPECTRUM MORTI

Confirmation No: 6890

Examiner: SCHUBERG, L. J.

Group: 1651

Comments (Title 37 CFR 1.8(a))
I hereby certify that the correspondence is being
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Sept. 11, 2001
Patent P.O. Box 1600, Alexandria, VA 22313-1600 on
Sept. 11, 2001
Ninety-Nine (99) minutes.
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17 CFR 1.112 DECLARATION

Via Facsimile No. 701-272-8100

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Commissioner for Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

I, Charles M. Lynne, declare as follows:

- I am one of the named inventors and am familiar with patent application No. 10748,637 entitled "INCREASING SPECTRUM MORTI" (hereafter the '637 application) and the subject matter described therein.

Sept. 12, 2006 1:49PM

No. 0421 P. 2

T-425 P. 25/40 F-718

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(Enclosure)

RULE 13.2 DECLARATION
for Application of Breaker N. L., et al.
Confirmation No: 6390
Application No: 10748.637
Page - 2 -

2. I hold an MD and am board certified in Urology. I am presently employed as a Professor of Urology at the University of Miami Miller School of Medicine. I have worked in the field of Urology for 15 years.

3. I have authored or coauthored more than 70 scientific papers.

4. I have reviewed the Office Action dated June 13, 2006 and references cited therein. I have been asked by patent counsel Zacharias to provide an explanation based on the claimed invention showing that the subject matter of the claims differs from the cited art.

Independent claim 1 is copied below.

Claim 1. A method of increasing motility of sperm, the method comprising the steps of:

- providing from a subject a biological sample comprising sperm and at least one epithelium; and
- contacting the biological sample with an agent that maintains or reduces the biological activity of the at least one epithelium selected from the group consisting of TNFa, IL-1 β , and IL-6.

5. The Examiner has rejected claims 1, 2, 5, 6, 8-19 are rejected under 35 U.S.C. §102(b) as being anticipated by Alexander et al. (US 6,180,355 B1). The Examiner has also rejected claims 1, 6 and 8-19 under 35 U.S.C. §103(a) as being unpatentable over Alexander et al. (US 6,180,355 B1) in view of Bauler et al. (Journal of Andrology 2002). Claims 1, 2, and 5.

respectfully

RULE 172 DECLARATION
In re Application of: Bruckett N. L., et al.
Confirmation No: 6830
Application No.: 10743,637
Page - 3 -

19 were rejected under 35 U.S.C. § 101(a) as being unpatentable over Alexander et al. (US 6,180,355 B1) in view of Esther et al. (Obstetrics and Gynecology 2001) and Slesarch (US 5,834,439).

6. First, I will discuss the Alexander et al. (US 6,180,355 B1) reference and why this patient does not teach or disclose the instant invention.

The Alexander patent discusses the use of cytokines as indicators to help diagnose chronic pelvic pain syndrome (CPPS). Simply put, Alexander discusses that cytokines in the seminal plasma can be used as "indicators or confirmatory indicators" of CPPS or an associated disorder. Alexander defines CPPS as the presence of leukocytosis in the expressed prostate secretions or by analysis found in a urine sample obtained following a prostate massage. Alexander interchanges the terms "CPPS" and "chronic prostatitis" in the text of their patent. Alexander discusses the condition(s) with respect to sexual function.

Alexander discusses a "method of treating a condition associated with elevated levels of a cytokine, such as TNF-alpha, in seminal plasma, comprising administering a therapeutically effective amount of one or more cytokine...," Further, all treatments taught in this Alexander patent are by systemic administration of oral or parenteral agents.

The instant invention is not taught or disclosed by Alexander et al.

11/2006

Sept. 12, 2006 1:49PM

No. 0421 P. 4
T-425 P. 27/40 F-719

5616596313

SEP-13-06 04:52PM FORM-AMERICAN SENTERFITT

The Examiner wrongly interprets Alexander's teaching, i.e., the Examiner assumes that effect on sexual function also occurs to fertility. The Examiner's assumption is not supported by any facts or examples in the Alexander patent, nor is this assumption correct in the medical field. Our patient addresses low sperm motility, not a condition of sexual dysfunction.

As described, Alexander uses cytokines as "indicators or confirmatory indicators" of CPPS. In contrast to the Alexander patent, our patient does not use cytokines to diagnose a disease. Instead, our patient states that cytokines are signs in the semen which act immediately on sperm cells to reduce their motility in the ejaculate. Prior to contact with the semen cytokines, sperm motility is normal or near normal.

Alexander discusses a "method of treating a condition associated with elevated levels of a cytokine, such as TNF-alpha, in seminal plasma, comprising administering a therapeutically effective amount of an anti-cytokine...". The "condition" clearly referred to in the Alexander patent is CPPS or a similar condition, not the presence of the cytokines themselves, as is the case in our patient. Our target group is not men with CPPS, but men with spinal cord injury. Our patient does not claim that CPPS causes decreased sperm motility.

All treatments taught in the Alexander patent are by systemic administration of oral or parenteral agents. In the Alexander patent, there is no provision for treating the semen. In the

invention

Sept. 12, 2006 1:49PM

1-425 P. 28/40 F-719

5616596313

SEP-13-06 04:52PM FORM-14-GERMAN CENTERFITT

RULE 112 DECLARATION
In re Application of: Donald N. L. et al.
Confirmation No: 63940
Application No.: 10748,617
Page: 1 -

5. In the medical field, there is no basis for assuming that treating the semen will improve CPS. Our patent provides for treating the semen to improve the condition of low sperm motility in men with spinal cord injury.

7. Second, I will discuss the Basu et al. reference and why this reference does not teach or disclose the instant invention.

Some of the Examiner's objections are based on publications by Basu. The Examiner believes that these Basu publications precluded the patent application. Basu is one of our co-inventors. It is my understanding that the invention discloses date is the key date. This invention disclosure was submitted to the University of Miami on July 11, 2002. The date of conception as listed on the invention Disclosure form was Jan. 12, 2001. The examiner asserts that "one of ordinary skill in the art would have been motivated to use the method of Alexander because Alexander discloses that the method can be used to treat conditions associated with elevated levels of a cytokine."

Once again, we assert that the method referred to treat conditions such as CPPS by administration of anti cytokine agents orally or parenterally. Our method treats an unrelated condition, low sperm motility, by the addition anti cytokine agents to the seminal plasma *in vitro* (see above).

11/12/2006

Sept. 12, 2006 1:49PM
No. 0421 P. 6

SEP-13-06 04:52PM FORM-ACKERMAN SENTERFITT
T-425 P.29/40 F-718

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5616586313 DURATION (mm:ss) 05:06

ROUTE 132 DECLARATION
in re Application of: Brackett N. L., et al.
Confirmation No: 6890
Application No.: 10778617

8. Third, I will discuss the Taber et al. reference and why this reference does not teach or discuss the instant invention. This reference discusses the occurrence of certain cytotoxicities in the peritoneal fluid of women, with endometriosis and their effect on the binding of sperm to this zona pellucida. It discusses infertility in women caused or related to endometriosis.

The latest investigation is 100 times more accurate than Fricker et al.

Fowler does not measure or evaluate sperm motility. It measures the interaction of sperm with a certain portion of the ovum and notes that women with endometriosis may have elevated levels of cypatines in their peritoneal fluid and fallopian tubes that may interfere with sperm-zona binding. There is no suggestion on their part or reasonable medical conclusion that can be reached that teaches that treating sperm in the ejaculate will or may remedy this affliction of the female reproductive tract.

The examiner states that peritoneal fluid is produced from the reproductive tract. This is

9. Fourth, I will discuss the Treasury references and why their reference does not teach or disclose the incident invention. This reference discusses the system's effects of TMR-alpha in a variety of trade and other legal conditions as well as pre-term failure and the role of a certain enzymatic dipeptidase (ChD01) in modulating these effects, specifically the synthesis of

113

RULS 172 DECLARATION
In re Application of: Bracken N. L., et al.
Confirmation No: 6390
Application No.: 10748,637
Page 7 -

prostaglandin E2. This prostaglandin peptide is a component of the bacterial cell wall of normal vaginal flora and may also be found in human amniotic fluid.

The instant invention is not taught or disclosed by Slesarev et al:

Neither male infertility nor low sperm motility or any other sperm disease motility is mentioned or suggested in the discussion of the effects of TNF-alpha or the modulation of its effects. Slesarev proposed the vaginal application of GM600 as a treatment of pre term labor and of "pregnancy toxicity". In another instance, the vaginal application seems to be included with all other methods of administration, (oral, topical, rectal, and/or a food supplement) in various systemic absorptior. In this setting, we do not agree that "use of ordinary skill in the art would have had a reasonable expectation of success [in treating low sperm motility by our method] because Slesarev had previously administered vaginally a compound that inhibits TNF-alpha". Again, we propose treating a local condition, low sperm motility, rather than a systemic condition.

10. I further state that all statements made herein are of my own knowledge are true and that all statements made are information and belief are believed to be true, and further that these statements were made with my knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United

MPR/MS/MS

Sept. 12, 2006 1:49PM
No. 0421 P. 8

SEP-13-06 04:52PM FORM-AGREEMENT SENTERFITT T-425 P. 31/40 F-718

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RULE 112 DECLARATION

In re Application of: Breckell N. L. et al.
Confirmation No: 68910
Application No: 10748,637
Page - 8 -

States Code, and that such willful false statements may jeopardize his validity on two separate counts.

Charles M. Lyons

Dr. Charles M. Lyman

9/11/2026

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No. 0421 P. 9

T-425 P.32/40 F-719

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Sept. 12. 2006 1:50PM

EXHIBIT "A"

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Brackett N. L., et al.

Confirmation No: 6890

Application No.: 10/748,637

Examiner: SCHUBERG, L. J.

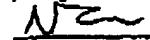
Date Filed: December 30, 2003

Group: 1651

For: INCREASING SPERM MOTILITY

CERTIFICATE UNDER 37 CFR 1.8(a)
I hereby certify that this correspondence is being
deposited either by facsimile to 571-273-8300 or with
the U.S. Postal Service as First Class mail in an envelope
addressed to Mail Stop Amendment, Commissioner for
Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on

Sept 13, 2006

 Reg. No. 56,712
Nicholae A. Zacharias37 C.F.R. 1.132 DECLARATIONVia Facsimile No. 571-273-8300

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Daniel R. Cohen, declare as follows:

1. I am one of the named inventors and am familiar with patent application No. 10/748,637 entitled "INCREASING SPERM MOTILITY" (hereafter the '637 application) and the subject matter described therein.

2. I hold a Medical Doctor degree in Gynecology and a Medical Doctor degree in Medical Genetics. I am presently employed as Medical Director at Second Medical Opinion Services-Gracias Doctor Corporation & American Health National Network-. I have worked in

{WP333253;1}

RULE 132 DECLARATION

In re Application of: Brackett N. L., et al.
Confirmation No: 6890
Application No.: 10/748,637
Page - 2 -

the field of prenatal diagnosis of genetic diseases, cytogenetics and molecular biology (Northern Blot, Southern Blot, mitochondrial DNA sequencing, and microarray DNA technology

3. I have authored or coauthored more than 11 scientific papers, and one patent.

in Argentina (Continue cloning keratinocytes stem cell system for skin culture)

4. I have reviewed the Office Action dated June 13, 2006 and references cited therein. I have been asked by patent counsel Zachariades to provide an explanation based on the claimed invention showing that the subject matter of the claims differs from the cited art.

Independent claim 1 is copied below.

Claim 1. A method of increasing motility of sperm, the method comprising the steps of:

- a) providing from a subject a biological sample comprising sperm and at least one cytokine; and
- b) contacting the biological sample with an agent that inactivates or reduces the biological activity of the at least one cytokine selected from the group consisting of TNF α , IL1 β , and IL6.

5. The Examiner has rejected claims 1, 2, 5, 6, 8-19 are rejected under 35 U.S.C. §102(b) as being anticipated by Alexander *et al.* (US 6,180,355 B1). The Examiner has also rejected claims 1-6 and 8-19 under 35 U.S.C. §103(a) as being unpatentable over Alexander *et al.* (US 6,180,355 B1) in view of Basu *et al.* (*Journal of Andrology* 2002). Claims 1, 2, and 5-

{WP333253:1}

RULE 132 DECLARATION

In re Application of: Bracken N. L., et al.
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19 were rejected under 35 U.S.C. §103(a) as being unpatentable over Alexander *et al.* (US 6,180,355 B1) in view of Faber *et al.* (Obstetrics and Gynecology 2001) and Slesarev (US 5,834,435).

6. First, I will discuss the Alexander *et al.* (US 6,180,355 B1) reference and why this patent does not teach or disclose the instant invention.

The Alexander patent discusses the use of cytokines as indicators to help diagnose chronic pelvic pain syndrome (CPPS). Simply put, Alexander discusses that cytokines in the seminal plasma can be used as "indicators or confirmatory indicators" of CPPS or an associated disorder. Alexander defines CPPS as the presence of leukocytosis in the expressed prostatic secretions or by sediment found in a urine sample excreted following a prostate massage. Alexander interchanges the terms "CPPS" and "chronic prostatitis" in the text of their patent. Alexander discusses the condition(s) with respect to sexual function.

Alexander discusses a "method of treating a condition associated with elevated levels of a cytokine, such as TNF-alpha, in seminal plasma, comprising administering a therapeutically effective amount of an anti-cytokine..." Further, all treatments taught in the Alexander patent are by systemic administration of oral or parenteral agents.

The instant invention is not taught or disclosed by Alexander *et al.*

(WP333253.1)

RULE 132 DECLARATION

In re Application of: Brackett N. L., et al.
Confirmation No: 6890
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Page - 4 -

The Examiner wrongly interprets Alexander's teaching, i.e., the Examiner assumes that effects on sexual function also occur to fertility. The Examiner's assumption is not supported by any facts or examples in the Alexander patent, nor is this assumption correct in the medical field. Our patent addresses low sperm motility, not a condition of sexual dysfunction.

As described, Alexander uses cytokines as "indicators or confirmatory indicators" of CPPS. In contrast to the Alexander patent, our patent does not use cytokines to diagnose a disease. Instead, our patent states that cytokines are agents in the semen which act immediately on sperm cells to reduce their motility in the ejaculate. Prior to contact with the semen cytokines, sperm motility is normal or near normal.

Alexander discusses a "method of treating a condition associated with elevated levels of a cytokine, such as TNF-alpha, in seminal plasma, comprising administering a therapeutically effective amount of an anti-cytokine..." The "condition" clearly referred to in the Alexander patent is CPPS or a similar condition, not the presence of the cytokines themselves, as is the case in our patent. Our target group is not men with CPPS, but men with spinal cord injury. Our patent does not claim that CPPS causes decreased sperm motility.

All treatments taught in the Alexander patent are by *systemic administration* of oral or parenteral agents. In the Alexander patent, there is no provision for treating the semen. In the

(WP933253;1)

RULE 132 DECLARATION

In re Application of: Brackett N. L., et al.
Confirmation No: 6890
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Page - 5 -

medical field, there is no basis for assuming that treating the semen will improve CPPS. Our patent provides for treating the semen to improve the condition of low sperm motility in men with spinal cord injury.

7. Second, I will discuss the Basu *et al.* reference and why this reference does not teach or disclose the instant invention.

Some of the Examiner's objections are based on publications by Basu. The Examiner believes that these Basu publications preceded the patent application. Basu is one of our co-inventors. It is my understanding that the invention disclosure date is the key date. The invention disclosure was submitted to the University of Miami on July 31, 2002. The date of conception as listed on the Invention Disclosure form was Jan. 12, 2001. The examiner asserts that "one of ordinary skill in the art would have been motivated to use the method of Alexander because Alexander discusses that the method can be used to treat conditions associated with elevated levels of a cytokine....."

Once again, we assert that the method referred to treats conditions such as CPPS by administration of anti cytokine agents orally or parenterally. Our method treats an unrelated condition, low sperm motility, by the addition anti cytokine agents to the seminal plasma in vitro (see above).

(WP333253;1)

RULE 132 DECLARATION

In re Application of: Brackett N. L., et al.

Confirmation No: 6890

Application No.: 10/748,637

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8. Third, I will discuss the Faber *et al.* reference and why this reference does not teach or disclose the instant invention. The reference discusses the occurrence of certain cytokines in the peritoneal fluid of women with endometriosis and their effect on the binding of sperm to the zona pelluoida. It discusses infertility in *women* caused or related to endometriosis.

The instant invention is not taught or disclosed by Faber *et al.*

Faber does not measure or evaluate sperm motility. It measures the interaction of sperm with a certain portion of the ovum and notes that women with endometriosis may have elevated levels of cytokines in their peritoneal fluid and fallopian tubes that may interfere with sperm - zona binding. There is no suggestion on their part or reasonable medical conclusion that can be reached that teaches that treating sperm in the ejaculate will or may remedy this affliction of the *female reproductive tract*.

The examiner states that peritoneal fluid is produced from the reproductive tract. This is factually incorrect.

9. Fourth, I will discuss the Slesarev reference and why this reference does not teach or disclose the instant invention. The reference discusses the systemic effects of TNF-alpha in a variety of toxic and often fatal conditions as well as pre term labor and the role of a certain muramyl dipeptide (GMDP) in modulating these effects, specifically the synthesis of

(WP333253:1)

RULE 132 DECLARATION

In re Application of: Brackett N. L., et al.
Confirmation No: 6890
Application No.: 10/748,637
Page - 7 -

prostaglandin E2. This probiotic muramyl peptide is a component of the bacterial cell wall of normal vaginal flora and may also be found in human amniotic fluid.

The instant invention is not taught or disclosed by Slesarev *et al.*

Neither male infertility nor low sperm motility or any other sperm abnormality is mentioned or suggested in the discussion of the effects of TNF-alpha or the modulation of its effects. Slesarev proposed the vaginal application of GMFD as a treatment of pre term labor and of "pregnancy toxicity". In another instance, the vaginal application seems to be included with all other methods of administration, (oral, topical, rectal, and as a food supplement) to achieve systemic absorption. In this setting, we do not agree that "one of ordinary skill in the art would have had a reasonable expectation of success [in treating low sperm motility by our method] because Slesarev had previously administered vaginally a compound that inhibits TNF-alpha". Again, we propose treating a local condition, low sperm motility, rather than a systemic condition.

10. I further state that all statements made herein are of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with my knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United

(WP333253;1)

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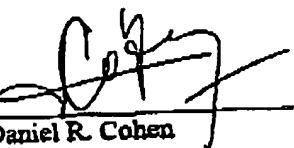
PAGE 08

RULE 132 DECLARATION

In re Application of: Bracken N. L., et al.
Confirmation No: 6890
Application No.: 10/748,637
Page - 8 -

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States Code, and that such willful false statements may jeopardize the validity of the application
or any patent issued thereon.



Dr. Daniel R. Cohen

9-12-2006

Date

(WP333253:1)